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DEVELOPMENT OF THE AFFINE MOLECULE TO CIS PROTEIN BY METHODS OF STRUCTURE-BASED DRUG DESIGN

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CIS protein – is a protein of the SOCS-family and it plays very important role in the regulation of the JAK/STAT signalling pathway. This pathway controls immune response and CIS can block it by interaction with phosphorilated tyrosine (pTyr) [1]. The main role in this interaction belongs to SH2-domain, which is conservative for the SOCS-family. Therefore, if we develop the small molecule, which can bind with the SH2-domain effectively, we can achieve the enhancing of the immune response, especially towards tumors [2]. Moreover, such a molecule can be successfully used as a linker in the PROTAC technology, whish supposes the connection of the impaired protein to another one that can interact with the ubiquitin ligase. This process leads to the following degradation of the impaired protein into the proteasome. In the case of CIS protein this interaction can be caused by interaction with elongin B/C, which also plays important role in the interaction of CIS with JAK-kinase and influence on the possibility of its binding to pTyr [3].

The aims of the study were: 1) to develop the 3D-structure of CIS as it is still remains unknown, while the sequence of aminoacids does exist; 2) to analyze interaction of CIS with elongin B/C to suggest the way CIS can be influenced by it; 3) to develop the molecule that could effectively inhibit the interaction between CIS and pTyr in order to stop the negative regulation of the pathway caused by CIS.

The 3D-structure of CIS was designed with the help of different on-line services (Swiss Model, ModWeb, IntFOLD2 etc.) based on the homology modelling.

Other steps were performed with the help of Maestro tools, ver. 2016-4 (Schrödinger). First, we optimized the selected structure by adding absent atoms and editing side chains. Then minimizatiom was performed to find the most energetically favorable state of the molecule. To analyze the interaction between CIS and elongin B/C we used molecular dynamics. We compared dynamics of CIS with the dynamics of complex of CIS and elongin B/C. To develop the inhibitor of CIS we detected the binding pocket of pTyr and found out, which aminoacids participated in the interaction with pTyr. Then we used the lybrary of different heterocycles to perform the docking and to create the small molecule on the basis of the docking results.

Finally, at the present moment we have achieved the following results: 1) the 3D-structure of CIS was selected; 2) the assesment of the interaction “CIS-elongin B/C” was performed; 3) the scaffold of the inhibitor was designed by virtual screening.

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